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SYNTHETIC APPROACH TO STEMODIN---A NOVEL STEREOCONTROLLED CONSTRUCTION OF THE STEMODANE SYSTEM BY THE SUCCESSIVE INTRAMOLECULAR DIELS-ALDER REACTIONS

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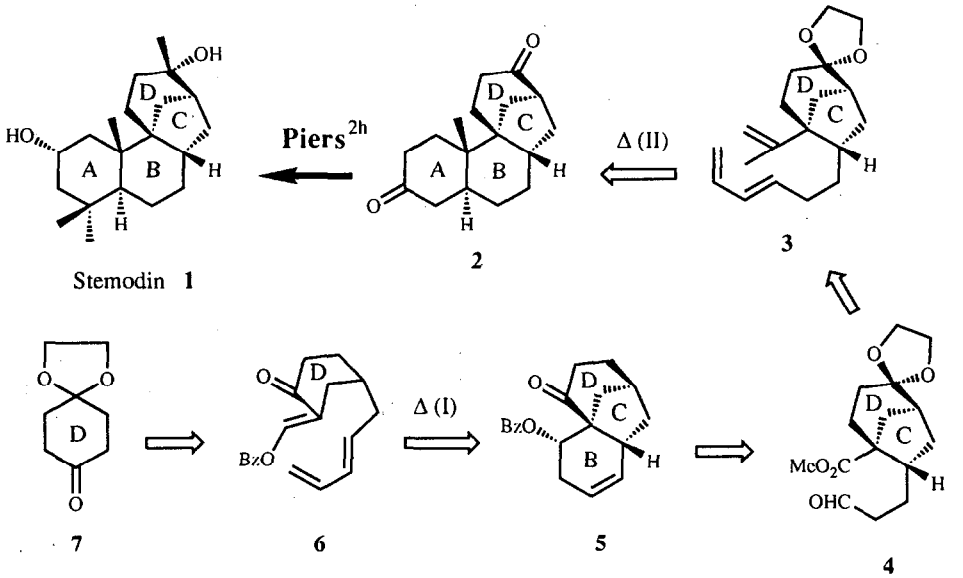
Abstract: The tetracyclic compound **18**, possessing the stemodane skeleton, was synthesized from 1,4-cyclohexanedione monoethylene ketal **7**. The key steps, **6**→**5** and **16**→**18**, involve intramolecular Diels-Alder reaction.

Because of unique carbon skeleton and alleged medicinal properties of *Stemodia maritima* L.,[1] the stemodane group of diterpenoids has received considerable attention as targets for synthesis.[2] Herein we report an efficient synthesis of the stemodane nucleus **18**, as part of a study directed toward the total synthesis of stemodin **1**. Our strategy based upon the synthetic analysis is shown below. Namely, the intramolecular Diels-Alder reaction of the triene **6**, obtained from **7**, would give the tricyclic ketone **5**, which could be transformed into **3** *via* the aldehyde **4**. The second intramolecular Diels-Alder reaction of **3** would afford the tetracyclic compound **2**, convertible into stemodin **1**.

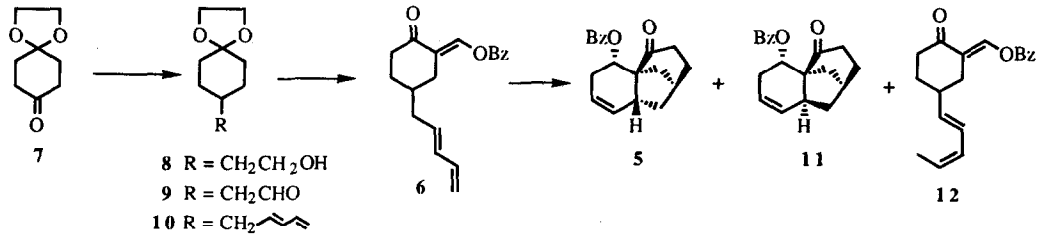
Scheme 1



In order to explore the feasibility of the designed synthetic strategy, stereocontrolled synthesis of **18** was first examined as a model experiment for the construction of **2**. The requisite triene **6** for the initial Diels-Alder reaction was readily prepared as described below. A commercially available **7** was converted into the alcohol **8** in the usual manner (1. $(EtO)_2P(O)CH_2CO_2Et$ / NaH in DME, 2. H_2 / 10% Pd-C in EtOAc, 3. LAH in THF, 95% overall yield), which was followed by oxidation[3] with SO_3·Py / DMSO in the presence of Et_3N to afford the aldehyde **9** (77%). Selective preparation of the (E)-dienes, developed by Yamamoto[4]

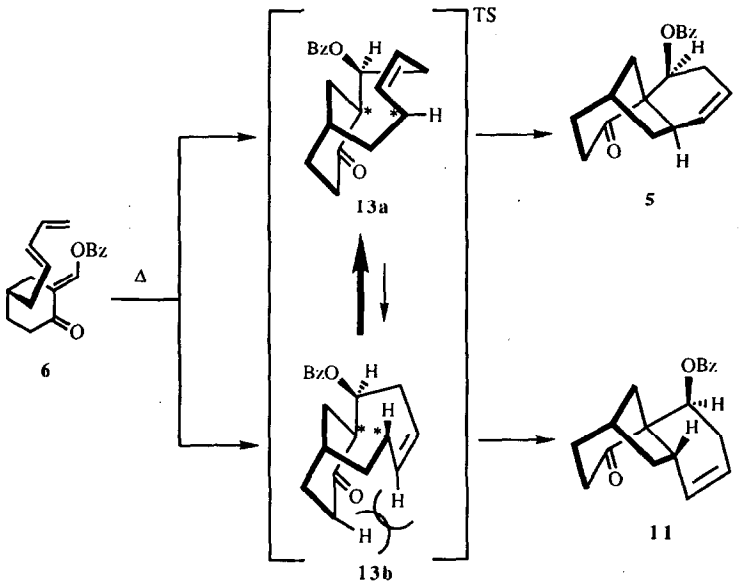
($Ph_2P(O)CH_2CH{=}CH_2$ / ^nBuLi / HMPA in THF), was applied to **9** to give rise to **10** (61%),[5] which was converted into the triene **6** in three steps (1. 10% $HClO_4$ in THF, 2. HCO_2Et / NaH in C_6H_6, 3. Bz_2O / Py / DMAP in CH_2Cl_2, 87%). Heating **6** in the presence of a catalytic amount of methylene blue[6] in *o*-dichlorobenzene at 180 °C for 6 h produced a mixture of two tetracyclic compounds (**5** and **11**) and the isomerization product **12**[7] (70%) in a ratio of 7 : 1 : 0.5. The structure of the major component **5** was determined by X-ray analysis.[8]

Scheme 2



The preferred formation of **5** could be due to a "concerted but nonsynchronous" transition state for the cyclization.[6b,9] The steric congestion between the olefinic hydrogen and the axial hydrogen in the nine membered ring transition state **13b**, first partially formed, makes it less favorable than the alternative transition state **13a** which affords the desired product **5**.

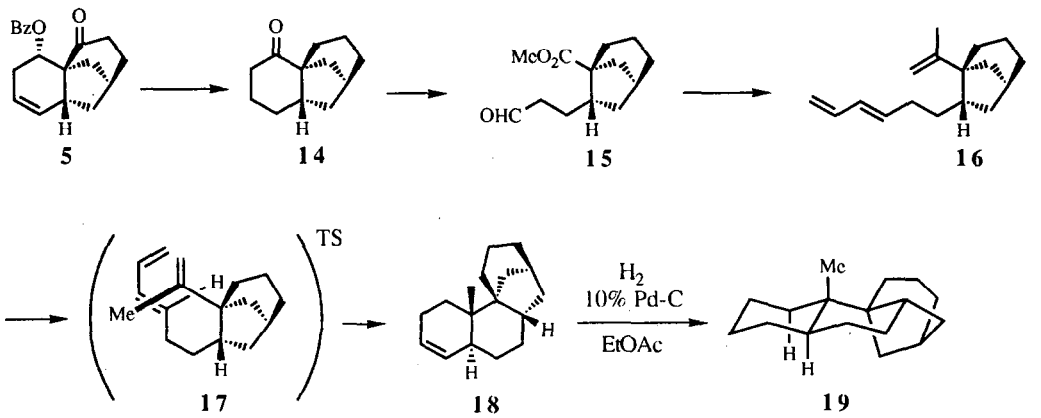
Figure 1



Our synthetic efforts were next focused on the ring opening and subsequent introduction of diene and dienophile portions for the second intramolecular Diels-Alder reaction. Toward this end, the carbonyl moiety of **5** was removed by Wolff-Kishner reduction[10] and the resulting alcohol was transformed into the ketone **14** in two steps (1. H_2 / 10% Pd-C in EtOAc, 2. PCC / SiO_2 in CH_2Cl_2, 68%). The treatment of **14** with Vedejs' reagent[11] in THF (-78°C, 1.5 h), followed by oxidation with $Pb(OAc)_4$ in MeOH-C_6H_6(1:3 v/v) at 0°C for 1.5 h gave **15** (35 %). After Wittig reaction in the same manner as previously, transformation of the resulting ester to the triene **16** was carried out by two steps, methylation with MeLi (28%)[12] and dehydration with $SOCl_2$ in Py (86%). An

intramolecular Diels-Alder reaction was conducted in the presence of methylene blue[6] in toluene at 220 °C for 96 h in a sealed tube to produce the tetracyclic compound **18** in 89% yield as a single product. The stereochemistry of **18** was deduced on the preference of the exo-conformer **17** in the transition state during the thermolysis and the spectral evidence of **19**; particularly due to the similarity of the half-band width (Wh/2=1.00 Hz) of the angular methyl group with the proposed[13] that (Wh/2=0.91 Hz) of the methyl group possessing two anticoplanar protons at the C_{10} position in *trans*-decalin derivatives.

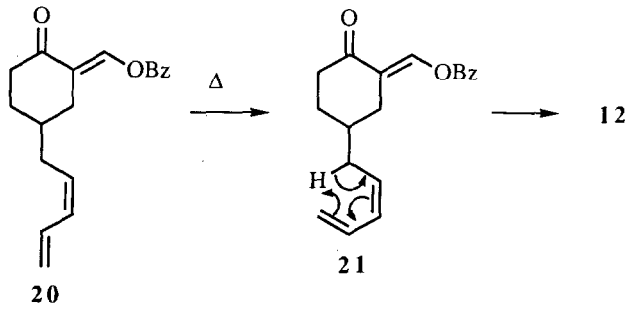
Scheme 3



Application of this novel methodology to the synthesis of stemodin **1** is in progress.

References and Notes

1. (a) P. S. Manchand, J. D. White, H. Wright, and J. Clardy, *J. Am. Chem. Soc.*, **95**, 2705 (1973); (b) C. D. Hufford, R. Guerro, and N. J. Doorenbos, *J. Pharm. Sci.*, **65**, 778 (1976).
2. (a) S. Chatterjee, *J. Chem. Soc., Chem. Commun.*, 622 (1979); (b) E. J. Corey, M. A. Tius, and J. Das, *J. Am. Chem. Soc.*, **102**, 7613 (1980); (c) E. E. van Tamelen, J. G. Carlson, R. K. Russell, and S. R. Zawachy, *J. Am. Chem. Soc.*, **103**, 4615 (1981); (d) R. B. Kelly, M. L. Harley, S. J. Alward, R. N. Rej, G. Gowda, and A. Mukhopadhyay, *Can. J. Chem.*, **61**, 269 (1983). (e) R. B. kelly, S. Lal, G. Gowda, and R. N. Rej, *Can. J. Chem.*, **62**, 1930 (1984). (f) R. M. Bettolo, P. Tagliatesta, A. Lupi, and D. Bravetti, *Helv. Chim. Acta*, **66**, 760 (1983); (g) J. D. White and T. C. Somers, *J. Am. Chem. Soc.*, **109**, 4424 (1987); (h) E. Piers, B. F. Abeysekera, D. J. Herbert, and I. D. Suckling, *J. Chem. Soc., Chem. Commun.*, 404 (1982); *idem*, *Can. J. Chem.*, **63**, 3418 (1985); (i) J. Germanas, C. Aubert, and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **113**, 4006 (1991).
3. J. R. Parikh and W. E. Doering, *J. Am. Chem. Soc.*, **89**, 5505 (1967).
4. J. Ukai, Y. Ikeda, N. Ikeda, and H. Yamamoto, *Tetrahedron Lett.*, **24**, 4029 (1983).
5. E / Z ratio (17:1) was determined after the initial intramolecular Diels-Alder reaction (**6** → **5** + **11** + **12**).
6. (a) D. F. Taber and S. A. Saleh, *J. Am. Chem. Soc.*, **102**, 5085 (1980); (b) D. F. Taber, C. Campbell, B. P. Gunn, and I-C. Chiu, *Tetrahedron Lett.*, **22**, 5141 (1981).
7. The compound **12** was obtained through 1,5-sigmatropic rearrangement of **20** under the thermal conditions.

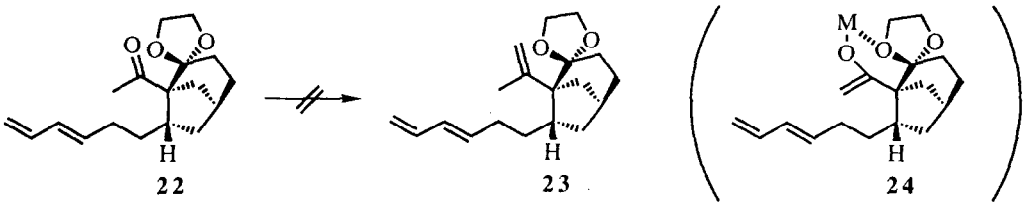


20 21

8. The compound **5** crystalizes in the monoclinic $P2_1/n$ space group with a=10.743 (1), b=12.322 (3), c=12.108 (1) Å, α=90.0, β=90.719 (12), γ=90.0°, V=1602.8 (4), and Z=4. The final coordinates were solved by direct methods and refined by block diagonal least squares methods with R=0.071, Rw=0.062. Final crystallographic coordinates are deposited in Cambridge Crystallographic Data Center.

9. E. Ciganek, *Organic Reactions*, **32**, 1 (1984), and refs cited therein.

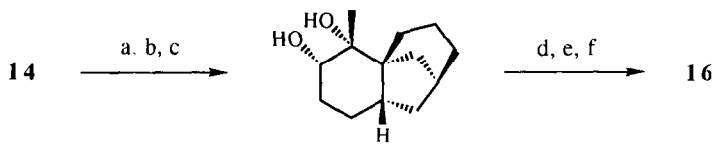
10. All attemps (a: $Ph_3P^+MeBr^-$, ^nBuLi; b: CH_2Br_2, Zn, $TiCl_4$; c: MeLi, hexane then $SOCl_2$) in the conversion (**22**→**23**) led to failure, and the starting material **22** was recovered unchanged probably due to the metal chelated intermediate **24**.



22 23 24

11. E. Vedejs, *J. Am. Chem. Soc.*, **96**, 5944 (1974).

12. By using different synthetic route shown below, it is possible to obtain fair yield of the triene **16**.



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Reagents and reaction conditions

a) MeLi, hexane; b) $SOCl_2$, Py; c) OsO_4, NMO, Et_2O, H_2O, 33% from **14**, d) $NaIO_4$, Et_2O, H_2O; e) $Ph_2P(O)CH_2CH{=}CH_2$, ^nBuLi, THF, HMPA; f) $Ph_3P^+MeBr^-$, ^nBuLi, DME, 39% from **25**.

13. K. L. Williamson, T. Howell, and T. A. Spencer, *J. Am. Chem. Soc.*, **88**, 325 (1966).

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